REVIEW ARTICLE

Medication-related osteonecrosis of the jaw

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Abstract

In 2014, the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) was changed in medication-related osteonecrosis of the jaw (MRONJ) to include osteonecrosis of the jaw caused by non-bisphosphonates (BPs) drugs. MRONJs are a rare drug adverse reaction associated with BPs and other antiresorptive (denosumab) and antiangiogenetic therapies. MRONJ pathophysiology is not completely elucidated, and three risk factors should be considered: Local factors, underlying disease and kind of medication. MRONJ affects considerably patient's quality of life, so it is important to know pathology and risk factor in order to prevent or treat immediately the disease. Various BRONJ staging systems are used by clinicians: In 2006 Ruggero *at al.* proposed a clinical staging system with three different levels based on signs and symthoms; in 2009 American Association of Oral and Maxillofacial Surgeons implemented it with Stage 0. Marx in 2007 was the only one who divided the stages on the basis of the lesion's size. Bedogni in 2012 proposed a clinical-radiological staging system. The aim of this review is to summarize the current diagnosis, prevention and treatment strategies.

Keywords: Bisphosphonate-related osteonecrosis of the jaw, medication-related osteonecrosis of the jaw, osteoporosis

Introduction

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) changed the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) into medication-related osteonecrosis of the jaw (MRONJ), to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenetic therapies.[1] MRONJ affects considerably patient's quality of life, so it's important to know pathology and risk factor in order to prevent or treat immediately the disease. The aim of this review is to represent the current knowledge about MRONJ: Prevention, diagnosis and treatment strategies.

Related Medications and Risk Factors

Two pharmacological agents are involved in the ONJ process: Both antiresorptive (Bisphosphonates [BPs] and RANK-L inhibitors) and antiangiogenetic drugs (Table 1, Table 2).

Antiresorptive

BPs can be classified into aminobisphosphonates (NBPs) and non-aminobisphosphonates (non-NBPs) on the basis of an amino functional group presence, NBPs are the one involved in the osteonecrosis of the jaw.

NBPs can be administrated orally or as intravenous (IV) drugs:

- IV BPs are used in the management of cancer-related conditions, including hypercalcemia of malignancy, skeletal-related events associated with bone metastases of solid tumor such as breast cancer, prostate cancer, and lung cancer and for multiple myeloma.[2-14]
- Oral BPs are prescribed for osteoporosis,[15,16] osteopenia[17] or other less common conditions (Paget's disease and osteogenesis imperfect).[18,19]
- RANK ligand inhibitor (denosumab) is an antiresorptive medication used in patients affected by osteoporosis or metastatic bone disease, which inhibits osteoclast function, decreases bone resorption and increases bone density.[20,21]

Antiangiogenetic

A class of drugs, which interferes with the formation of new blood vessels, is blocking the angiogenesis signaling cascade.

Monoclonal antibodies stop receptor or growth factor (bevacizumab) while small molecules determine the block by binding the tyrosine kinase receptor (Sunitinib and Sorafenib), facilitating the other anticancer agents delivery.[22]

MRONJ pathophysiology is not completely elucidated.[23-26] Its unique localization to the jaws may be explained by several hypothesis: Inflammation or infection, microtrauma, altereted bone remodeling, or oversuppression of bone resorption, angiogenesis inhibition, soft tissue BPs toxicity, a peculiar biofilm of the oral cavity, terminal vascularization of the mandible, suppression of immunity or Vitamin D deficiency.[23,27-36]

Table 1: MRONJ related medications

Molecule	Category	Indication
Alendronate	Bisphosphonate	Osteoporosis
Risedronate	Bisphosphonate	Osteoporosis
Ibandronate	Bisphosphonate	Osteoporosis
Neridronate	Bisphosphonate	Osteogenesis imperfect Paget's disease of bone
Pamidronate	Bisphosphonate	Bone metastases
Zolendronate	Bisphosphonate	Bone metastases Osteoporosis
Tiludronate	Bisphosphonate	Paget's disease of bone
Denosumab	RANK-L inhibitors	Bone metastases Osteoporosis
Sunitib	Tyrosine kinase inhibitors	GIST, RCC, pNET
Sorafenib	Tyrosine kinase inhibitors	HCC, RCC
Bevacizumab	Humanized monoclonal antibody	mCRC, NSCLC, Glio, mRCC
Sirolimus	Mammalian target of rapamycin pathway	Organ rejection in renal transplant

GIST: Gastrointestinal stromal tumor, RCC: Renal cell carcinoma; pNET: Pancreatic neuroendocrine tumor, HCC: Hepatocellular carcinoma, mCRC: Metastatic colorectal carcinoma, NSCLC: Non-squamous non-small cell lung carcinoma, Glio: Glioblastoma, mRCC: Metastatic renal cell carcinoma, MRONJ: Medication-related osteonecrosis of the jaw

Three risk factors should be considered: Local factors, underlying disease and kind of medication.

Age, sex, use of alcohol and tobacco are all individual risk factors that may be associated with other systemic factors or concurrent pathologies such as diabetes, rheumatoid arthritis, dialysis, anemia, hypocalcemia, immunosuppression, and osteomalacia. Local risk factors include microtrauma, oral surgery, removable prosthesis, anatomic conditions such as tori and oral implantology. Medication-related risk factors, which should be considered, are the molecule, the way of administration and the length of therapy. To explain disease frequency, we have to consider two criterions: Therapeutic indications (osteoporosis/osteopenia and malignancy) and type of medication (BP and non-BP). Exposition to zolendronate in cancer patients leads to ONJ risk 50-100 times higher than cancer patients treated with placebo. Even if the ONJ risk is similar in patients treated by denosumab, it's important to underline a substantial difference between BRONJ and denosumab-related osteonecrosis of the jaw (DRONJ). BRONJ occurs after a mean administration of 33 months (IV in cancer patients) or 48 months (OS in osteporotic patients). DRONJ occurs early after treatment, independently of the number of previous administrations. Hence, ONJ risk after use of RANK-L inhibitors decreases monthly, while for bisphosphonate drugs remains stable for years. The risk of BRONJ is directly related to the duration of the therapy and total amount of the medications.[37-39]

Table 2: Different BRONJ staging systems

Stage	Marx 2007[49]	Ruggiero *et al.*[2]	Bedogni[36]
At risk category		No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	
Stage 0	Subclinical damage, microscopically represented by beginner hypocellularity osteoclast apoptosis and decrease of endosteal osteoblast	Nonspecific clinical findings and symptoms such as jawpain or osteosclerosis but no clinical evidence of exposed bone	
Stage 1	A: Painless exposed bone <1 cm B: Painless exposed bone >1 cm	Exposed/necrotic bone in patients who are asymptomatic and who have no evidence of infection	Focal BRONJ Clinical signs and symptoms: bone exposure; sudden dental mobility; nonhealing postextraction socket; mucosal fistula; swelling; abscess formation; trismus; gross mandibular deformity; and/or hypoesthesia/paraesthesia of the lips CT finding: increased bone density limited to the alveolar bone region (trabecular thickening and/or focal osteosclerosis), with or without the following signs: markedly thickened and sclerotic lamina dura; persisting alveolar socket; and/or cortical disruption: 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)

(Cond..)

Table 2: *(Continued...)*

Stage	Marx 2007[49]	Ruggiero *et al.*[2]	Bedogni[36]
Stage 2	A: Painful and infected single exposed bone <2 cm B: Painful and infected single exposed bone >2 cm	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Diffuse BRONJ Clinical signs and symptoms: the same as Stage 1 CT findings: increased bone density extended to the basal bone (diffuse osteosclerosis), with or without the following signs: prominence of the inferior alveolar nerve canal; periosteal reaction; sinusitis; sequestra formation; and/or oroantral fistula: 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge)
Stage 3	A: Multiple exposed bone areas without clinical findings of osteolysis, orocutaneous fistula, or pathological fractures B: Exposed bone >3 cm or with clinical findings of osteolysis, or orocutaneous fistula, or pathological fractures	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor	Complicated BRONJ The same as Stage 2, with one or more of the following: clinical signs and symptoms: extraoral fistula; displaced mandibular stumps; nasal leakage of fluids CT findings: Osteosclerosis of adjacent bones (zygoma, hard palate); pathologic mandibular fracture; and/or osteolysis extending to the sinus floor

BRONJ: Bisphosphonate-related osteonecrosis of the jaw, AAOMS: American Association of Oral and Maxillofacial Surgeons, SICMF: Italian Society for Maxillofacial Surgery, SIPMO: Italian Society of Oral Pathology and Medicine, IV: Intravenous, CT: Computed tomography

Table 3: Prevention strategies

Cancer patients before starting IV medical treatment	Asymptomatic cancer patients receiving IV medical treatment	Osteoporotic patients before starting oral medical treatment	Osteoporotic patients receiving oral medical treatment
Inadequate dentures should be modified, rebased or replaced. Patients should achieve a proper oral hygiene and be instructed to report any pain, swelling or exposed bone. If allowed by systemic conditions, initiation of antiresorptive or antiangiogenetic therapy should be delayed until oral health is stable or, at least, until the extraction site has mucosalized (2-3 weeks) or until an adequate osseous healing	A good oral hygiene is essential to prevent dental infections that may require dentoalveolar surgery. Indeed, every invasive procedure that involves bone injury should be avoided. Non-restorable teeth should be treated by removal of the crown and endodontic treatment of the remaining roots. Dental implants placement should be avoided	Starting treatment, patients should be educated to the risk of MRONJ. The importance of oral hygiene and dental health should be underlined	(1) Patients treated with oral-NBP for less than 4 years without risk factors No modification or delay of surgery is necessary (2) Patients treated with oral-NBP for less than 4 years and corticosteroids or antiangiogenetic drugs concurrently The prescriber should be contacted to evaluate a drug holiday for at least 2 months before oral surgery (3) Patients treated with oral-NBP for more than 4 years The prescriber should be contacted to evaluate a drug holiday for at least 2 months before oral surgery

IV: Intravenous

Definition and Staging Systems

According to the last definition by AAOMS in 2014, Patients are affected by MRONJ if all the following clinical manifestations are demonstrated:

1. Current or previous therapy with antiresorptive or antiangiogenetic drugs;[2]
2. No patient history of radiation therapy or manifest metastatic disease to the jaw;
3. Exposed bone or presence of an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks.

However, there is no unanimous consensus on point three, because the exposed necrotic bone in the oral cavity is just one of the possible manifestations of BRONJ and it is not found in all patients.

In 2012, the Italian Society for Maxillofacial Surgery and the Italian Society of Oral Pathology and Medicine proposed a new definition:[37] "BRONJ is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible or maxilla of patients exposed to the treatment with nitrogen-containing BPs, in the absence of a previous radiation treatment." Only 76% of BRONJ were diagnosed based on the AAOMS definition: Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed.

Various BRONJ staging systems are used by clinicians: In 2006 Ruggero *et al.*[33] proposed a clinical staging system with three different levels based on signs and symthoms; in 2009, AAOMS implemented it with Stage 0.[2] Marx[35] in 2007 was the

Table 4: Treatment strategies

Patients about to start IV medical treatment	Patients receiving IV medical treatment	Patients receiving oral NBPs by less than 4 years	Patients receiving oral NBPs by more than 4 years
Oral health examination			
Clinical examination Radiological examination General and oral health record	Follow-up program with regular check-ups every 4-6 months Orthopantomography every 6-12 months Dental cone beam CT if the orthopantomography is uncertain	Follow-up program with regular check-ups every 6 months Orthopantomography just in case of MRONJ signs and symptoms Dental cone beam CT if the orthopantomography is uncertain	Follow-up program with regular visits once every 4-6 months Orthopantomogram just in case of MRONJ signs and symptoms Dental cone beam CT if the orthopantomography is uncertain
Oral health achievement/ conservation			
Extraction of partial embedded teeth or those with poor prognosis Extraction of mobile deciduous teeth in children Periodontal stabilization splints for teeth with a grade 1-2 mobility in patients with a good dental hygiene; extraction in patients with a poor dental hygiene Conservative, endodontic and prosthodontics therapy of teeth with good prognosis Mandibular or maxillary tori removal, especially if multilobate and/or with great dimensions Adjust, rebase or replace inadequate removable denture to decrease the oral tissue pressure and to prevent sore spots, especially along the lingual flange region or at the tori Local risk factors elimination (i.e. inadequate conservative or prosthodontics restorations)	Endodontic procedures should be preferred to dental surgery Endodontic procedures should be completed without any osseous injury Every conventional procedure of restorative dentistry or prosthodontics could be completed Local fluoride administration Scaling and root planning Periodontal stabilization splints for teeth with a grade 1-2 mobility in patients with a good dental hygiene; extraction in patients with a poor dental hygiene It should be carefully assess the possibility of a GBR/GTR procedure due to an antiangiogenic effect of NBP therapy In case of implantology, the patient should be informed about the possibility of long-term MRONJ	Endodontic procedures should be preferred to dental surgery Endodontic procedures should be completed without any osseous injury Every conventional procedure of restorative dentistry or prosthodontics could be completed Local fluoride administration Scaling and root planning Periodontal stabilization splints for teeth with a grade 1-2 mobility in patients with a good dental hygiene; extraction in patients with a poor dental hygiene It should be carefully assess the possibility of a GBR/ GTR procedure due to an antiangiogenic effect of NBP therapy In case of implantology, the patient should be informed about the possibility of a long-term MRONJ Extraction of teeth with a grade 3 mobility and/or endodontal-periodontal lesions	Endodontic procedures should be preferred to dental surgery Endodontic procedures should be completed without any osseous injury Every conventional procedure of restorative dentistry or prosthodontics could be completed Local fluoride administration Risk factors elimination Scaling and root planning Periodontal stabilization splints for teeth with a grade 1-2 mobility without endodontic/periodontal lesions Implant placement is possible but the patient should be informed about the possibility of a short and long term MRONJ Avoid using anesthesia with vasoconstrictor agents Extraction of teeth with a grade 3 mobility and/or endodontal-periodontal lesions is indicated. After an antibiotic prophylaxis, the surgical procedure should be executed with the lowes possible bone injury. All the granulation tissue should be removed and a primary closure is necessary
Adequate oral hygiene achievement			
Scaling and root planning Chlorhexidine 0.12% oral rinse (7 days/month) Oral hygiene instruction and motivation	Chlorhexidine 0.12% oral rinse (60 s/2 times a day for 7 days/ month) Risk factors elimination Adjust, rebase or replace inadequate removable denture to decrease the oral tissue pressure and to prevent sore spots, especially along the lingual flange region or at the tori	Chlorhexidine 0.12% oral rinse (60 s/2 times a day for 7 days/ month) Risk factors elimination Adjust, rebase or replace inadequate removable denture to decrease the oral tissue pressure and to prevent sore spots, especially along the lingual flange region or at the tori	Chlorhexidine 0.12% oral rinse (60 s/2 times a day for 7 days/month) Adjust, rebase or replace inadequate removable denture to decrease the oral tissue pressure and to prevent sore spots, especially along the lingual flange region or at the tori In case of fixed prosthodontics, the biological width should be respected
Medical treatment management			

(Cond..)

Table 4: *(Continued...)*

Patients about to start IV medical treatment	Patients receiving IV medical treatment	Patients receiving oral NBPs by less than 4 years	Patients receiving oral NBPs by more than 4 years
Instruction for avoiding every elective dental procedure or invasive surgery that involve direct osseous injury during the medical treatment and, at least, the first 5 years after the medical treatment Periodic clinical-radiological follow-up, the frequency of which is based on the way of medical administration, the number of risk factors and oral health status of patient	Oral hygiene instruction and motivation Informative and educational documents Instruction to quickly report every signs and symptoms Periodic clinical-radiological follow-up Before starting any procedure that involves bone, patient should be informed of the potential risk of MRONJ	Oral hygiene instruction and motivation Informative and educational documents Instruction to quickly report every signs and symptoms Obtain the informed consent Periodic clinical-radiological follow-up, the frequency of which is based on the way of medical administration, the number of risk factors and oral health status of patient Before starting any procedure that involves bone, patient should be informed of the potential risk of MRONJ	Oral hygiene instruction and motivation Informative and educational documents Instruction to quickly report every signs and symptoms Obtain the informed consent Instruction to avoid any osseous surgical procedures during and after the therapy Periodic clinical-radiological follow-up, the frequency of which is based on the way of medical administration, the number of risk factors and oral health status of the patient. It should be continued for at least 5 years after the termination of the medical administration Before starting any procedure that involves bone, patient should be informed of the potential risk of MRONJ

MRONJ: Medication-related osteonecrosis of the jaw, GBR: Guided bone regeneration, GTR: Guided tissue regenerative, NBP: Aminobisphosphonates, CT: Computed tomography, IV: Intravenous

only one who divided the stages on the basis of the lesion's size. Bedogni *et al.*[37] in 2012 proposed a clinical-radiological staging system.

Prevention of MRONJ

Dental screenings and adequate treatment are fundamental in order to reduce ONJ risk in patients under antiresorptive or antiangiogenetic therapy, or before starting the administration [Table 3].

The risk of ONJ increases when the duration of therapy exceeded 4 years. However, the risk of MRONJ in patients treated with oral BPs is lower compared to subjects treated with IV medications.

Conclusions

Treatment of ONJs is a demanding challenge for clinicians and an effective and appropriate MRONJ therapy is still to be decided, its strategies are described in Table 4.

The choice between a conservative treatment and surgery is not easy, and it should be made on a case by case basis. However, the initial approach should be as conservative as possible.

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